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EXAMINER	
CHEN, SHIN LIN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,400	COLLINS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-61* is/are pending in the application.

4a) Of the above claim(s) *9-14, 20-24, 27-54, 57, 60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,15-19,25,26,55,56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-24-08 has been entered.

Applicants' amendment filed on 12-21-07 has been entered. Claims 1, 8 and 25 have been amended. Claims 2 and 7 have been canceled. Claims 1, 3-6 and 8-61 are pending. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are under consideration.

It should be noted group IV was elected in the reply filed on 11-27-06. The amended claim 1 read on partial or complete deletion of one or more rHMPV SH, G, M2-1, M2-2, or M2 ORFs or one or more nucleotide substitutions that reduces or ablates expression of the one or more rHMPV SH, G, M2-1, M2-2, or M2 ORFs. However, the elected subject matter of group IV is "an isolated recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising one or more nucleotide substitution that reduces or ablates expression of rHMPV M2-2 ORF such that a wild type M2-2 protein is not produced, and a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P) and a large polymerase protein (L), and an expression vector comprising the partial or complete rHMPV genome or antigenome under the control of a promoter". Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Therefore, only the subject matter of "a

rHMPV comprising one or more attenuating nucleotide modification or comprising one or more nucleotide substitution that reduces or ablates expression of **rHMPV M2-2 ORF**" and claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are under consideration.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 55 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on naturally occurring HMPV, which is not patentable. HMPV itself can be considered as an expression vector and the HMPV contains a transcriptional promoter and a transcriptional terminator.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15-19, 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "[t]he rHMPV of claim 7" in line 1 of claim 15 is vague and renders the claim indefinite. Claim 7 has been canceled. Claim 15 depends from a canceled claim. It is unclear what is intended to claim. Claims 16, 17 and 58 depend from claim 15.

The phrase "[t]he rHMPV of claim 7" in line 1 of claim 18 is vague and renders the claim indefinite. Claim 7 has been canceled. Claim 18 depends from a canceled claim. It is unclear what is intended to claim. Claim 59 depends from claim 18.

The phrase "[t]he rHMPV of claim 7" in line 1 of claim 19 is vague and renders the claim indefinite. Claim 7 has been canceled. Claim 19 depends from a canceled claim. It is unclear what is intended to claim.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. The claims encompass a genus of various rHMPV strains and substrains having different nucleotide sequences.

The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2). The claims encompass a genus of structural variants of SEQ ID No. 1 or 2, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the variants that one skilled in the art can envision the nucleotide sequence of any other HMPV strain or substrain. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. It is apparent that applicants only have possession of the nucleotide sequence of HMPV strain 83 and strain 75 but do NOT have possession of nucleotide sequence of any other HMPV strains or substrains. The nucleotide sequences of SEQ ID Nos. 1 and 2 are insufficient to describe the claimed recombinant HMPVs.

The claims also read on one or more attenuating modification comprising deleting or substituting the nucleotide sequence of M2-2 ORF of any HMPV that reduces or ablates expression. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The claims read on not only complete deletion of M2-2 ORF but also partial deletion, substitution and other type of modification of the M2-2 ORF. The claims encompass various modified nucleotide sequences encoding a genus of numerous structural variants of the amino acid sequence encoded by the disclosed M2-2 ORF, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The

specification fails to provide the structural features of the variant proteins and the biological function of the variant proteins was unpredictable at the time of the invention (discussed below). The specification also fails to provide guidance for whether those variant proteins could result in the phenotypic change as recited in the claims. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the amino acid sequence encoded by the M2-2 ORF as disclosed in the present application is insufficient to describe the genus. The nucleotide sequence of the disclosed M2-2 ORF is insufficient to describe the claimed recombinant HMPVs.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed recombinant HMPVs and expression vector comprising said HMPVs. Thus, it is concluded that the written description requirement is not satisfied for the recombinant HMPVs and expression vector comprising said HMPVs as claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the disclosed sequences referred to above, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argue that the specification fully describes the claimed invention and exemplified two strains of HMPV, operability of the invention is independent of the fine details of the nucleotide sequence of the HMPV strain (amendment, p. 11-12). This is not found persuasive because of the reasons set forth above. HMPV was first repoted by Van der Hooen et al. in 2001 and only the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2) were known at the time of the invention. The claims encompass a genus of structural variants of SEQ ID No. 1 or 2 but no other HMPV strains and nucleotide

sequence encoding M2-2 proteins have been disclosed. It is apparent that applicants do not have possession of the full scope of the HMPV as claimed. The claims also read on one or more attenuating modification comprising deleting or substituting the nucleotide sequence of M2-2 ORF of any HMPV that reduces or ablates expression or the modified M2-2 ORF results in claimed phenotype. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide the structural features of the variant proteins and the biological function of the variant proteins was unpredictable at the time of the invention (discussed below). Absent specific guidance, one skilled in the art at the time of the invention would not known what deletion, substitution or other modification of the M2-2 ORF would reduce expression of the M2-2 ORF or result in the claimed phenotypes. Thus, operability of the invention is relevant to the fine details of the nucleotide sequence of the HMPV strain.

7. Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant HMPV lacking M2-2 ORF as disclosed in the specification, wherein rHMPV lacking M2-2 ORF (ΔM2-2) replicates more than 10-fold less efficiently than wild type HMPV in LLC-MK2 cells and the ΔM2-2 mutant HMPV is more sensitive to interferon as compared to wild type rHMPV-GFP, does not reasonably provide enablement for any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF

or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV, wherein said rHMPV results in the phenotypic change recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 1, 3-6, 8, 15-19, 25, 26, 58 and 59 are directed to an attenuated, replication competent recombinant human metapneumovirus (rHMPV) comprising a partial or complete

recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable heterologous sequence endogen a polypeptide, such as a reporter. Claim 5 specifies the reporter comprises GFP. Claim 6 specifies the detectable heterologous sequence is operably linked to HMPV transcription gene start and gene end signal. Claim 8 specifies the M2-2 functional protein is not produced. Claims 15 and 16 specify the one or more attenuating nucleotide modifications comprises one or more nucleotide substitution that reduces or ablates expression of a rHMPV M2-2 ORF or further comprises one or more substitution that ablates one or more potential translation initiation codons of the rHMPV M2-2 ORF or introduces one or more in-frame stop codons into the rHMPV M2-2 ORF. Claims 17 and 19 specify the rHMPV sequence of SEQ ID No. 1 and rHMPV M2-2 ORF of SEQ ID No. 1, respectively. Claim 25 specifies the one or more attenuating nucleotide modifications produce the recited desired phenotypic change in the rHMPV. Claims 58 and 59 specify the rHMPV demonstrates a ten-fold or more reduction in growth in the presence of interferon. Claims 55 and 56 are directed to an expression vector comprising an operably linked transcriptional promoter, a partial or complete recombinant rHMPV genome or antigenome, and a transcriptional terminator, wherein the rHMPV genome or antigenome comprises one or more attenuating nucleotide modifications.

The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2) (e.g. p. 16). The specification discloses that the

rHMPV lacking M2-2 ORF (ΔM2-2) replicates more than 10-fold less efficiently than wild type HMPV in LLC-MK2 cells, however, in Vero cells the ΔM2-2 mutant grows to a final titer that equals or exceeds that of wild type HMPV. One important difference between LLC-MK2 and Vero cells is that the latter lack the structural genes for type I interferon. The ΔM2-2 mutant HMPV is more sensitive to interferon as compared to wild type rHMPV-GFP (e.g. p. 79-80). The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. As discussed above, it is apparent that applicants only have possession of the nucleotide sequence of HMPV strain 83 and strain 75 but do NOT have possession of nucleotide sequence of any other HMPV strains or substrains. Absent possession of the claimed rHMPV other than the disclosed SEQ ID Nos. 1 and 2, one skilled in the art at the time of the invention would not know how to use the claimed rHMPV without undue experimentation.

The claims encompass various rHMPV strains and substrains comprising one or more attenuating modification comprising deleting, substituting or other modification of the nucleotide sequence of M2-2 ORF of any HMPV. The claimed attenuated, replication competent rHMPV must have a use. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide adequate guidance and evidence for the

biological functions of various variant M2-2 proteins encoded by the modified M2-2 ORF sequence comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and whether and what kind of phenotypic change of the rHMPV could be resulted by said modification.

It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different

functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The biological function of the attenuated or modified M2-2 protein would affect the resulting phenotype of the claimed rHMPV. The specification fails to provide adequate guidance and evidence for the biological function of various M2-2 variant proteins and fails to provide specific guidance for whether and how those various modifications of M2-2 ORF would result in any phenotypic change or the claimed phenotypic change of rHMPV in vitro or in vivo. In view of the unpredictable biological function of a protein from mere amino acid sequence and the lack of guidance regarding the phenotypic change of the rHMPV resulted from various modifications of M2-2 ORF, one skilled in the art at the time of the invention would not know how to use the full scope of the claimed rHMPVs in vitro or in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that complete deletion of M2-2 ORF results in an attenuated phenotype of the virus, one of ordinary skill in the art would understand that mutations in the viral genome would result in a decline in activity of the M2-2 ORF, although possibly to a degree different

than that by complete deletion of the M2-2 ORF. The specification teaches how to make any particular mutation in the HMPV viral genome and how to test such mutated viruses for a suitable degree of attenuation of replication, and the statement of specification must be taken as objectively correct (amendment, p. 12-13). This is not found persuasive because of the reasons set forth above under first paragraph enablement rejection. The claims encompass various rHMPV strains and substrains comprising one or more attenuating modification comprising deleting, substituting or other modification of the nucleotide sequence of M2-2 ORF of any HMPV. The claimed attenuated, replication competent rHMPV must have a use. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The specification fails to provide adequate guidance and evidence for the biological functions of various variant M2-2 proteins encoded by the modified M2-2 ORF sequence comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and whether and what kind of phenotypic change of the rHMPV could be resulted by said modification.

The specification only shows that the rHMPV lacking M2-2 ORF (ΔM2-2) replicates more than 10-fold less efficiently than wild type HMPV in LLC-MK2 cells and the ΔM2-2 mutant HMPV is more sensitive to interferon as compared to wild type rHMPV-GFP. Although it was known how to make mutant HMPV and how to test the activity of HMPV, however, the biological functions of numerous HMPV M2-2 variant proteins were unpredictable at the time of the invention and it was unpredictable what would be the resulting phenotype of those HMPV

mutants. Although the complete deletion of M2-2 ORF results in 10-fold less efficient replication and more sensitive to interferon as compared to wild type, however, the specification fails to provide enabling disclosure for whether the complete deletion, partial deletion, substitution or other modification of the M2-2 ORF would result in the recited phenotype, such as a change in growth properties in cell culture, a change in growth properties or virulence in the upper or lower respiratory tract of a mammalian host, a change in viral plaque size, a change in sensitivity or adaptation to temperature, a change in cytopathic effect, a change in efficiency of transcription, a change in the efficiency of expression of one or more genes, a change in immunogenicity, and attenuated viral growth by about 50-100 fold or greater. The specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed. The particular phenotype of the rHMPV lacking M2-2 ORF (ΔM2-2) does not make the resulting phenotype of numerous different rHMPV mutants having diverse M2-2 ORF mutations predictable. One skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 3, 4, 6, 8, 15, 16, 18, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS).

Claims 1, 3, 4, 6, 8, 15, 16, 18, 55 and 56 are directed to an attenuated, replication competent recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable heterologous sequence endogen a polypeptide, such as a reporter. Claim 6 specifies the detectable heterologous sequence is operably linked to HMPV transcription gene start and gene end signal. Claim 8 specifies the M2-2 functional protein is not produced. Claims 15 and 16 specify the one or more attenuating nucleotide modifications comprises one or more nucleotide substitution that reduces or ablates expression of a rHMPV M2-2 ORF or further comprises one or more substitution that ablates one or more potential translation initiation codons of the rHMPV M2-2 ORF or introduces one or more in-frame stop codons into the

rHMPV M2-2 ORF. Claims 55 and 56 are directed to an expression vector comprising an operably linked transcriptional promoter, a partial or complete recombinant rHMPV genome or antigenome, and a transcriptional terminator, wherein the rHMPV genome or antigenome comprises one or more attenuating nucleotide modifications.

Bermingham teaches construction of the NdeI and K5 mutations, which interrupt M2 ORF2, of human respiratory syncytial virus (hRSV) by adding 2 nucleotides to codon 47 of M2-2 that results in 18 additional codons encoding non-M2-2 amino acids (NdeI mutation), and by changing codon 1, 3 and 7 of M2-2 ORF to ACG and introducing stop codons into all three reading frames immediately downstream of the M2-1 termination codon (K5 mutation) (e.g. Figure 1). The RSV transcription and RNA replication were studied by using a negative-sense RSV-chloramphenicol acetyltransferase (CAT) minigenome C2 containing the CAT ORF under the control of RSV transcription initiation and termination signals flanked by 3'-leader and 5'trailer regions of the RSV genome (e.g. p. 11260, right column, last paragraph). The minigenome C2 directs the synthesis of antigenome and CAT mRNA when it is complemented by N, P, and L. Bermingham shows that viable RSV was recovered in vitro even when expression of M2-2 is ablated. "Virus lacking M2-2 grew less efficiently than did the wild-type parent in vitro, with titers that were reduced 1,000-fold during the initial 2-5 days, and 10-fold by days 7-8. Compared with wild-type virus, the intracellular accumulation of RNA by M2-2 knockout virus was reduced 3- to 4-fold or more for genomic RNA and increased 2- to 4-fold or more for mRNA". Bermingham suggests that M2-2 mediates a regulatory "switch" from transcription to RNA replication and the M2-2 knockout virus has a highly desirable phenotype

for vaccine development because the virus growth is attenuated while gene expression is concomitantly increased (e.g. abstract).

Bermingham does not teach the nucleotide sequence of human metapneumovirus (hMPV).

Van den Hoogen (2001) teaches isolation and identification of human metapneumovirus and discloses the nucleotide sequence and amino acid sequences of the HMPV (e.g. abstract, Figure 3, p. 724, left column).

Van den Hoogen (2002) teaches that the clinical symptoms of human respiratory syncytial virus (human RSV) and human metapneumovirus (hMPV) are largely similar to the respiratory tract illnesses, and both hMPV and human RSV are members of Pneumovirinae subfamily (e.g. p. 119, left column). Van den Hoogen further compare M2-2 protein sequences from different penumoviruses (Figure 6B) and reports that the M2 gene is unique to the members of the Pneumovirinae subfamily and two overlapping ORFs have been observed in all pneumoviruses (e.g. p. 124, left column), and M2-2 ORFs are conserved in location but not in sequence and are thought to be involved in the control of the switch between virus RNA replication and transcription (e.g. p. 125, left column). For hMPV, the putative M2-2 ORF starts at nt 512 in the M2-1 ORF (Figure 1, p. 125, bridging left and right columns).

It would have been obvious for one of ordinary skill in the art at the time of the invention to construct a recombinant HMPV or an expression vector having a partial or complete HMPV genome or antigenome comprising one or more attenuating nucleotide modification of M2-2 as claimed because Bermingham teaches construction of such recombinant human RSV and van den Hoogen teaches the nucleotide sequence of HMPV, and both human RSV and HMPV are

members of Pneumovirinae subfamily and clinical symptoms for human RSV and HMPV are largely similar. Since M2-2 ORFs are conserved in location but not in sequence and are thought to be involved in the control of the switch between virus RNA replication and transcription, it would be obvious for one of ordinary skill in the art to prepare an attenuated HMPV having a mutated M2-2 protein with reasonable expectation of success in view of the teachings of Bermingham, Van den Hoogen (2001) and Van den Hoogen (2002). CAT gene is a type of reporter gene.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate a M2-2 knockout virus for vaccine development as taught by Bermingham with reasonable expectation f success.

11. Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS) as applied to claims 1, 3, 4, 6, 8, 15, 16, 18, 25, 55 and 56 above, and further in view of Ludin et al., 1996 (Gene, Vol. 173, p. 107-111).

Claims 1 and 3-5 are directed to an attenuated, replication competent recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein of a HMPV. Claims 3 and 4 specify the recombinant HMPV genome or antigenome further comprises a detectable

heterologous sequence endogen a polypeptide, such as a reporter. Claim 5 specifies the reporter comprises GFP.

The teachings of Bermingham, van den Hoogen (2001) and van den Hoogen (2002) are as discussed above.

Bermingham, van den Hoogen (2001) and van den Hoogen (2002) do not teach using green fluorescent protein (GFP) as a marker protein.

Ludin teaches preparation of novel vectors expressing fusion protein GFP-MAP2 or GFP-Tau34, which are fluorescent and both MAP2 and Tau34 are functional, to produce fluorescently tagged polypeptide for analysis of the function of those two microtubule-associated proteins and dynamic events in living cells (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to generate a recombinant HMPV expressing a GFP as a marker or a reporter because Ludin teaches preparation of novel vectors expressing GFP as a marker for analysis of the function and dynamic events in living cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to monitor the function of the fusion protein or dynamic events in living cells as taught by Ludin with reasonable expectation of success.

Applicants argue that claim 1 has been amended to include the limitation of claim 7, which was not included in the previous 103(a) rejection, therefore, the 35 U.S.C. 103(a) rejection is overcome. Applicants further argue that declaration by Dr. Peter Collin has been perfected (amendment, p. 13-14). This is not found persuasive because of the reasons set forth above

under 35 U.S.C. 103(a) rejection. Although the limitation of claim 7 has been included in amended claim 1, however, Bermingham generates mutant human respiratory syncytial virus (hRSV) that interrupt M2 ORF2 and shows that viable RSV was recovered in vitro even when expression of M2-2 is ablated. Dr. Peter Collin's declaration is discussed below.

Dr. Peter Collin's declaration argues that HMPV and RSV grow differently in culture, RSV has two additional genes NS1 and NS2, and protein bearing the same name among HMPV and RSV does not necessarily have same protein function. M2-1 and M2-2 proteins of HMPV and RSV have limited similarity. M2-1 protein is essential for RSV replication and its deletion is lethal, however, even M2-1 of HMPV has significant sequence relatedness with that of RSV and shares a cysteine-histidine motif, it was not essential for replication of HMPV. HMPV lacking both M2-1 and M2-1- replicated nearly as efficiently as wild type HMPV in cell culture. Since M2-2 had not sequence relatedness between HMPV and RSV, it would not be reasonable to anticipate results from M2-2. Dr. Collin further argues that HMPV and RSV are distinct viruses and they differ biologically, and Van den Hoogen only discloses partial HMPV sequence, which lacks the key promoter sequences, and it is not an authenticated, functional sequence that would produce a viable virus (declaration, p. 3-7). This is not found persuasive because of the reasons set forth above. Although HMPV and RSV are distinct viruses that differ biologically and M2-1 proteins of HMPV and RSV have different biological functions, however, both human RSV and HMPV are members of Pneumovirinae subfamily and clinical symptoms for human RSV and HMPV are largely similar. Since M2-2 ORFs are conserved in location but not in sequence and are thought to be involved in the control of the switch between virus RNA replication and transcription, it would be obvious for one of ordinary skill in the art to prepare an

attenuated HMPV having a mutated M2-2 protein in order to generate a M2-2 knockout virus for vaccine development with reasonable expectation of success in view of the teachings of Bermingham, Van den Hoogen (2001) and Van den Hoogen (2002). The claims read on an attenuated, replication competent recombinant HMPV having a mutated M2-2, in combination with N, P and L protein of a HMPV. Whether M2-2 protein of HMPV would have the same biological function as that of RSV and the result of attenuated M2-2 of HMPV would be predictable are irrelevant because the claims do not recite resulting phenotype changes of the attenuated HMPV and the teachings of Bermingham, Van den Hoogen (2001) and Van den Hoogen (2002) provide motivation and make it obvious for one of ordinary skill in the art to try the claimed invention. Van den Hoogen (2001) discloses 13350 bp of **complete genome** of human metapneumovirus isolate 00-1 (see GenBank Accession No. AF371337), which includes the ORFs of N, P, M2-2 and L proteins. Van den Hoogen (2002) discloses genomic map of HMPV isolate 00-1 and the putative ORFs of N, P, M2-2 and L proteins. It is unclear why the sequence disclosed by Van den Hoogen is considered partial sequence of the genome in Dr. Coolin's declaration. Dr. Collin's declaration states that the sequence disclosed by Van den Hoogen lacks key promoters but fails to point out what promoter is lacking such that no viable virus can be produced by one of ordinary skill in the art. The HMPV isolate 00-1 is viable virus and was propagated in tertiary monkey kidney cells. With the complete genomic sequence of HMPV at hand and known technology in making recombinant viruses and growing viable HMPV viruses, it would be obvious to one of ordinary skill in the art to practice the invention as claimed in the instant application.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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